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☐ 1. Document ID: WO 200136623 A2, AU 200136426 A

L1: Entry 1 of 1 File: DWPI May 25, 2001

DERWENT-ACC-NO: 2001-355632
DERWENT-WEEK: 200137
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TITLE: Novel recombinant adeno-associated virion consisting of nucleic acid (N) comprising transcriptional promoter region having ecdysone-responsive element linked to desired polynucleotide, or (N) encoding ecdysone receptor

Full | Title CIT.1 REV.1 CLS.1 REF.1 SEQ.1 ATT.1 RAW.1

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Term	Documents
RXR.DWPI,EPAB,JPAB,USPT,PGPB.	692
RXRS.DWPI,EPAB,JPAB,USPT,PGPB.	221
AAV.DWPI,EPAB,JPAB,USPT,PGPB.	1535
AAVS.DWPI,EPAB,JPAB,USPT,PGPB.	140
(RXR SAME AAV).USPT,PGPB,JPAB,EPAB,DWPI.	1
(RXR SAME AAV).USPT,PGPB,JPAB,EPAB,DWPI.	1

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Previous Page Next Page

WEST

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Search Results - Record(s) 1 through 10 of 11 returned.

☐ 1. Document ID: US 20020068815 A1

L3: Entry 1 of 11 File: PGPB Jun 6, 2002

PGPUB-DOCUMENT-NUMBER: 20020068815
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020068815 A1

TITLE: DAX-1 PROTEIN, METHODS FOR PRODUCTION AND USE THEREOF

PUBLICATION-DATE: June 6, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
MCCABE, EDWARD R. B.	PACIFIC PALISADES	CA	US	
GUO, WEIWEN	LOS ANGELES	CA	US	
BURRIS, THOMAS P.	GLEN GARDNER	NJ	US	
VILAIN, ERIC	LOS ANGELES	CA	US	

US-CL-CURRENT: 530/350; 435/69.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020049151 A1

L3: Entry 2 of 11 File: PGPB Apr 25, 2002

PGPUB-DOCUMENT-NUMBER: 20020049151
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020049151 A1

TITLE: Therapeutic approaches to diseases by suppression of the NURR subfamily of nuclear transcription factors

PUBLICATION-DATE: April 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Murphy, Evelyn	Dublin	TX	IE	
Conneely, Orla M.	Houston		US	
Fitzgerald, Oliver	Dublin		IE	
Bresnihan, Barry	Dublin		IE	

US-CL-CURRENT: 514/1; 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 20020004489 A1

L3: Entry 3 of 11 File: PGPB Jan 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020004489
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020004489 A1

TITLE: Retinoid receptor interacting polynucleotides, polypeptides, and antibodies

PUBLICATION-DATE: January 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Shi, Yanggu	Gaithersburg	MD	US	
Ruben, Steven M.	Olney	MD	US	

US-CL-CURRENT: 514/44; 435/325, 435/69.1, 530/350, 530/388.22, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 20010049144 A1

L3: Entry 4 of 11 File: PGPB Dec 6, 2001

PGPUB-DOCUMENT-NUMBER: 20010049144
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010049144 A1

TITLE: Methods for high level expression of genes in primates

PUBLICATION-DATE: December 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rivera, Victor	Arlington	MA	US	
Zoltick, Philip	Wynnewood	PA	US	
Wilson, James M.	Gladwyne	PA	US	

US-CL-CURRENT: 435/456; 424/93.21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 6406693 B1

L3: Entry 5 of 11 File: USPT Jun 18, 2002

US-PAT-NO: 6406693
DOCUMENT-IDENTIFIER: US 6406693 B1

TITLE: Cancer treatment methods using antibodies to aminophospholipids

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image | KWIC

☐ 6. Document ID: US 6342221 B1

L3: Entry 6 of 11 File: USPT Jan 29, 2002

US-PAT-NO: 6342221
DOCUMENT-IDENTIFIER: US 6342221 B1

TITLE: Antibody conjugate compositions for selectively inhibiting VEGF

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image | KWIC

☐ 7. Document ID: US 6342219 B1

L3: Entry 7 of 11 File: USPT Jan 29, 2002

US-PAT-NO: 6342219
DOCUMENT-IDENTIFIER: US 6342219 B1

TITLE: Antibody compositions for selectively inhibiting VEGF

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image | KWIC

☐ 8. Document ID: US 6312694 B1

L3: Entry 8 of 11 File: USPT Nov 6, 2001

US-PAT-NO: 6312694
DOCUMENT-IDENTIFIER: US 6312694 B1

TITLE: Cancer treatment methods using therapeutic conjugates that bind to aminophospholipids

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image | KWIC

☐ 9. Document ID: US 6214620 B1

L3: Entry 9 of 11 File: USPT Apr 10, 2001

US-PAT-NO: 6214620
DOCUMENT-IDENTIFIER: US 6214620 B1

TITLE: Inducible genetic suppression of cellular excitability

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image | KWIC

☐ 10. Document ID: US 6117680 A

L3: Entry 10 of 11 File: USPT Sep 12, 2000

US-PAT-NO: 6117680
DOCUMENT-IDENTIFIER: US 6117680 A

TITLE: Compositions and methods for regulation of transcription

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image | KWIC

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Term	Documents
(2 NOT 1).USPT,PGPB,JPAB,EPAB,DWPI.	11
(L2 NOT L1).USPT,PGPB,JPAB,EPAB,DWPI.	11

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Previous Page Next Page

WEST

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Search Results - Record(s) 11 through 11 of 11 returned.

☐ 11. Document ID: US 6015709 A

L3: Entry 11 of 11 File: USPT Jan 18, 2000

US-PAT-NO: 6015709
DOCUMENT-IDENTIFIER: US 6015709 A

TITLE: Transcriptional activators, and compositions and uses related thereto

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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Term	Documents
(2 NOT 1).USPT,PGPB,JPAB,EPAB,DWPI.	11
(L2 NOT L1).USPT,PGPB,JPAB,EPAB,DWPI.	11

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Previous Page Next Page

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L3: Entry 11 of 11 File: USPT Jan 18, 2000

DOCUMENT-IDENTIFIER: US 6015709 A
TITLE: Transcriptional activators, and compositions and uses related thereto

Brief Summary Paragraph Right (19):
Applications of this invention include transcription of genes, constitutively or in a drug-dependent manner in vitro, e.g. for the production of a desired protein which may be separately recovered, for achieving higher levels of expression in transcription based assays (including two-hybrid assays), and for the regulated expression of required viral genes in producer cells lines used for production of recombinant viruses (e.g. for the regulated expression of AAV rep and/or cap genes in host cells used for the production of recombinant AAV). Other applications include in vivo applications such as the constitutive or regulated expression of a target gene of interest in an animal model (e.g. for research or veterinary purposes) as well as for the constitutive or regulated expression of a target gene of interest in a human subject, e.g. in the case of gene therapy. In the case of human gene therapy, it will often be preferred that the components of the chimeric proteins be of human origin and/or that the engineered cells be encapsulated.

Detailed Description Paragraph Right (99):
The invention can be adapted to an ecdysone inducible system. Early work demonstrated that fusing the Drosophila steroid ecdysone (Ec) receptor (EcR) Ec-binding domain to heterologous DNA binding and activation domains, such as E. coli IexA and herpesvirus VP 16 permits ecdysone-dependent activation of target gen es downstream of appropriate binding sites (Christopherson et al. (1992) Proc. Natl. Acad. Sci. U.S.A. 89:6314). An improved ecdysone regulation system has been developed, using the DNA binding domain of the EcR itself. In this system, the regulating transcription factor is provided as two proteins: (1) a truncated, mutant EcR fused to herpes VP16 and (2) the mammalian homolog (RXR) of Ultraspiracle protein (USP), which heterodimerizes with the EcR (No et al. (1996) Proc. Natl. Acad. Sci. U.S.A. 93:3363). In this system, because the DNA binding domain was also recognized by a human receptor (the human farnesoid X receptor), it was altered to a site recognized only by the mutant EcR. Thus, the invention provides an ecdysone inducible system, in which a truncated mutant EcR is fused to at least one subunit of a transcriptional activator of the invention. The transcriptional activator further comprises USP, thereby providing high level induction of transcription of a target gene having the EcR target sequence, dependent on the presence of ecdysone.

Detailed Description Paragraph Right (121):
Yet another viral vector system useful for delivery of the subject chimeric genes is the adeno-associated virus (AAV). Adeno-associated virus is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review, see Muzyczka et al., Curr. Topics in Micro. and Immunol. (1992) 158:97-129). It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration (see for example Flotte et al., (1992) Am. J. Respir. Cell. Mol. Biol. 7:349-356; Samulski et al., (1989) J. Virol. 63:3822-3828; and McLaughlin et al., (1989) J. Virol. 62:1963-1973). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous DNA is limited to about 4.5 kb. An AAV vector such as that described in Tratschin et al., (1985) Mol. Cell. Biol. 5:3251-3260 can be used to introduce DNA into cells. A variety of nucleic acids have been introduced

into different cell types using AAV vectors (see for example Hermonat et al., (1984) PNAS USA 81:6466-6470; Tratschin et al., (1985) Mol. Cell. Biol. 4:2072-2081; Wondisford et al., (1988) Mol. Endocrinol. 2:32-39; Tratschin et al., (1984) J. Virol. 51:611-619; and Flotte et al., (1993) J. Biol. Chem. 268:3781-3790).

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L3: Entry 11 of 11 File: USPT Jan 18, 2000

US-PAT-NO: 6015709
DOCUMENT-IDENTIFIER: US 6015709 A

TITLE: Transcriptional activators, and compositions and uses related thereto

DATE-ISSUED: January 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
ARIAD Pharmaceuticals, Inc.	Cambridge	MA			02

APPL-NO: 8/ 920610 [PALM]
DATE FILED: August 27, 1997

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/918,401 entitled "Transcriptional Activators, and Compositions and Uses Thereto", filed Aug. 26, 1997, now abandoned.

INT-CL: [6] C12 N 1/15, C12 N 1/21, C12 N 5/10, C12 N 15/62

US-CL-ISSUED: 435/366; 435/252.3, 435/254.11, 435/325, 536/23.4
US-CL-CURRENT: 435/366; 435/252.3, 435/254.11, 435/325, 536/23.4

FIELD-OF-SEARCH: 435/252.3, 435/254.11, 435/325, 435/366, 536/23.1, 536/23.4, 935/33, 935/34, 935/36

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5573925	November 1996	Halazonetis	435/69.7
☐	5654168	August 1997	Bujard et al.	435/69.1

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0 685 493 A1	December 1994	EPX	
WO 93/14108	July 1993	WOX	
WO 97/08550	March 1997	WOX	
WO 97/31113	August 1997	WOX	
WO 97/44447	November 1997	WOX	

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Paal, K., "Basal Transcription Factors TBP and TFIB and the Viral Coactivator E1A 13S Bind with Distinct Affinities and Kinetics to the Transactivation Domain of NF-kB p65", Nucleic Acids Research, 25(5): 1050-1055 (1997).
Luo, Y., Mammalian Two-Hybrid System: A Complementary Approach to the Yeast Two-Hybrid System, BioTechniques, 22(2): 350-352 (1997).
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Le Douarin, B. et al., "A New Version of the Two-hybrid Assay for Detection of Protein-protein Interactions," Nucleic Acids Res., 23(5): 876-8 (1995).
Remacle J. E., et al., "Three Classes of Mammalian Transcription Activation Domain Stimulate Transcription in Schizosaccharomyces Pombe," EMBO J. ,16 (18): 5722-5729 (1997).
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Sublett, J., et al., "The Alveolar Rhabdomyosarcoma PAX3/FKHR Fusion Protein is a Transcriptional Activator," Oncogene, 11(3): 545-552 (1995).
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Tate, B. et al., "A Systematic Analysis of the AF-2 Domain of Human Retinoic Acid Receptor .alpha. Reveals Amino Acids Critical for Transcriptional Activation and Conformational Integrity", FASEB J., 10: 1524-1531 (1996).
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Schmitz, M. et al., "Transactivation Domain 2 (TA.sub.2) of p65 NF-.kappa.B", J. Biol. Chem., 270: 15576-15584 (1995).
Gerber et al. (1994) Transcriptional activation modulated by homopolymeric glutamine and proline stretches. Science 263:808-811, Feb. 1994.
Wang et al. (1997) Positive and negative regulation of gene expression in eukaryotic cells with an inducible transcriptional regulator. Gene Therapy 4:432-441, May 1997.

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ART-UNIT: 166
PRIMARY-EXAMINER: Degen; Nancy

ASSISTANT-EXAMINER: Schwartzman; Robert
ATTY-AGENT-FIRM: Berstein; David L. Hausdorff; Sharon F. Vincent; Matthew P.

ABSTRACT:

The present invention relates to chimeric transcriptional activators.

44 Claims, 20 Drawing figures

L3: Entry 10 of 11 File: USPT Sep 12, 2000

DOCUMENT-IDENTIFIER: US 6117680 A
TITLE: Compositions and methods for regulation of transcription

Brief Summary Paragraph Right (26):
Composition #3. Another such composition comprises a recombinant nucleic acid encoding a fusion protein comprising at least one ligand binding domain, bundling domain and transcription activation domain; a second recombinant nucleic acid encoding a protein comprising a DNA binding domain; and an optional third recombinant nucleic acid comprising a target gene (or cloning site) operatively linked to an expression control sequence including a DNA sequence recognized by the DNA binding domain mentioned above. Such compositions are illustrated by embodiments in which the ligand binding domains are or are derived from a receptor domain such as an ecdysone receptor; the DNA binding domain is or is derived from a DNA binding domain such as an RXR protein, chosen for its ability to bind to the receptor domain in the presence of a ligand for that receptor; the transcription activation domain is or is derived from an activation domain such as a VP16 or p65 domain; and the bundling domain is or is derived from a lac repressor tetramerization domain.

Brief Summary Paragraph Right (31):
Each of the recombinant nucleic acids of this invention may further comprise an expression control sequence operably linked to the coding sequence and may be provided within a DNA vector, e.g., for use in transducing prokaryotic or eukaryotic cells. Some or all of the recombinant nucleic acids of a given composition as described above, including any optional recombinant nucleic acids, may be present within a single vector or may be apportioned between two or more vectors. In certain embodiments, the vector or vectors are viral vectors useful for producing recombinant viruses containing one or more of the recombinant nucleic acids. The recombinant nucleic acids may be provided as inserts within one or more recombinant viruses which may be used, for example, to transduce cells in vitro or cells present within an organism, including a human or non-human mammalian subject. For example, the recombinant nucleic acids of any of Compositions 1-5, including any optional recombinant nucleic acids, may be present within a single recombinant virus or within a set of recombinant viruses, each of which containing one or more of the set of recombinant nucleic acids. Viruses useful for such embodiments include any virus useful for gene transfer, including adenoviruses, adeno-associated viruses (AAV), retroviruses, hybrid adenovirus-AAV, herpes viruses, lenti viruses, etc. In specific embodiments, the recombinant nucleic acid comprising the target gene is present in a first virus and one or more or the recombinant nucleic acids encoding the transcription regulatory protein(s) are present in one or more additional viruses. In such multiviral embodiments, a recombinant nucleic acid encoding a fusion protein comprising a bundling domain and a transcription activation domain, and optionally, a ligand binding domain, may be provided in the same recombinant virus as the target gene construct, or alternatively, on a third virus. It should be appreciated that non-viral approaches (naked DNA, liposomes or other lipid compositions, etc.) may be used to deliver recombinant nucleic acids of this invention to cells in a recipient organism.

Detailed Description Paragraph Right (88):
89:6314). An improved ecdysone regulation system has been developed, using the DNA binding domain of the EcR itself. In this system, the regulating transcription factor is provided as two proteins: (1) a truncated, mutant EcR fused to herpes VP16 and (2) the mammalian homolog (RXR) of Ultraspiracle protein (USP), which

heterodimerizes with the EcR (No et al. (1996) Proc. Natl. Acad. Sci. U.S.A. 93:3346). In this system, because the DNA binding domain was also recognized by a human receptor (the human farnesoid X receptor), it was altered to a site recognized only by the mutant EcR. Thus, the invention provides an ecdysone inducible system, in which a truncated mutant EcR is fused to at least one subunit of a transcription activator of the invention. The transcription factor further comprises USP, thereby providing high level induction of transcription of a target gene having the EcR target sequence, dependent on the presence of ecdysone.

Detailed Description Paragraph Right (96):
Regulated expression systems relevant to this invention involve the use of a protein containing a DNA binding domain to selectively target a desired gene for expression (or repression). Systems based on ligand-mediated cross-linking generally rely upon a fusion protein containing the DNA binding domain together with one or more ligand binding domains. One general advantage of such systems is that they are particularly modular in nature and lend themselves to a wide variety of design choices. These systems permit wide latitude in the choice of DNA binding domains. Many allostery-based systems, like the TetR- and progesterone-R-based systems, use a fusion protein containing a DNA binding domain together with a transcription regulatory domain (e.g. a transcription activation or repression domain). Some allostery-based systems such as the ecdysone-regulated system, use a protein like RXR which contains a DNA binding domain together with a binding site for another protein (such as the ecdysone receptor). Of the allostery-based systems, the progesterone receptor-based system and like systems permit relatively greater latitude in the choice of DNA binding domain. While allostery-based systems like the TetR- and ecdysone receptor type may be engineered at the DNA binding domain, they are somewhat less amenable to ready replacement of the DNA binding domain.

Detailed Description Paragraph Right (104):
A target gene construct comprises a gene of interest operably linked to an expression control sequence which permits ligand-regulated expression of the gene. More specifically, such a construct typically comprises: (1) one or more copies of a DNA sequence recognized by a DNA binding domain of a fusion protein of the invention (or by a DNA binding protein like RXR which binds to a fusion protein of the invention); (2) a promoter sequence consisting minimally of a TATA box and initiator sequence but optionally including other transcription factor binding sites; (3) sequence encoding the desired product, including sequences that promote the initiation and termination of translation, if appropriate; (4) an optional sequence consisting of a splice donor, splice acceptor, and intervening intron DNA; and (5) a sequence directing cleavage and polyadenylation of the resulting RNA transcript. Typically the construct contains a copy of the target gene to be expressed, operably linked to an expression control sequence comprising a minimal promoter and one or more copies of a DNA recognition sequence responsive to the transcription factor.

Detailed Description Paragraph Right (119):
In systems relying on a tetR or RXR-type DNA binding domain, the recognition sequence is again usually predetermined (by the choice of tetR or RXR-type DNA binding domain).

Detailed Description Paragraph Right (129):
The construct(s) once completed and demonstrated to have the appropriate sequences may then be introduced into a host cell by any convenient means. The constructs may be incorporated into vectors capable of episomal replication (e.g. BPV or EBV vectors) or into vectors designed for integration into the host cells' chromosomes. The constructs may be integrated and packaged into non-replicating, defective viral genomes like Adenovirus, Adeno-associated virus (AAV), or Herpes simplex virus (HSV) or others, including retroviral vectors, for infection or transduction into cells. Alternatively, the construct may be introduced by protoplast fusion, electroporation, biolistics, calcium phosphate transfection, lipofection, microinjection of DNA or the like. The host cells will in some cases be grown and expanded in culture before introduction of the construct(s), followed by the appropriate treatment for introduction of the construct(s) and integration of the construct(s). The cells will then be expanded and screened by virtue of a marker present in the constructs. Various markers which may be used successfully include hprt, neomycin resistance, thymidine kinase, hygromycin resistance, etc., and

various cell-surface markers such as Tac, CD8, CD3, Thy1 and the NGF receptor.

Detailed Description Paragraph Right (140):
Viral systems include those based on viruses such as adenovirus, adeno-associated virus, hybrid adeno-AAV, lentivirus and retroviruses, which allow for transduction by infection, and in some cases, integration of the virus or transgene into the host genome. See, for example, Dubensky et al. (1984) Proc. Natl. Acad. Sci. U.S.A. 81, 7529-7533; Kaneda et al., (1989) Science 243,375-378; Hiebert et al. (1989) Proc. Natl. Acad. Sci. U.S.A. 86, 3594-3598; Hatzoglu et al. (1990) J. Biol. Chem. 265, 17285-17293 and Ferry, et al. (1991) Proc. Natl. Acad. Sci. U.S.A. 88, 8377-8381. The virus may be administered by injection (e.g. intravascularly or intramuscularly), inhalation, or other parenteral mode. Non-viral delivery methods such as administration of the DNA via complexes with liposomes or by injection, catheter or biolistics may also be used. See e.g. WO 96/41865, PCT/US97/22454 and U.S. Ser. No. 60/084819, for example, for additional guidance on formulation and delivery of recombinant nucleic acids to cells and to organisms.

Detailed Description Paragraph Right (145):
In preferred embodiments of the invention, the subject expression constructs are derived by incorporation of the genetic construct(s) of interest into viral delivery systems including a recombinant retrovirus, adenovirus, adeno-associated virus (AAV), hybrid adenovirus/AAV, herpes virus or lentivirus (although other applications may be carried out using recombinant bacterial or eukaryotic plasmids). While various viral vectors may be used in the practice of this invention, AAV- and adenovirus-based approaches are of particular interest for the transfer of exogenous genes in vivo, particularly into humans and other mammals. The following additional guidance on the choice and use of viral vectors may be helpful to the practitioner, especially with respect to applications involving whole animals (including both human gene therapy and the development and use of animal model systems), whether ex vivo or in vivo.

Detailed Description Paragraph Right (156):
Another viral vector system useful for delivery of DNA is the adeno-associated virus (AAV). Adeno-associated virus is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review, see Muzyczka et al., Curr. Topics in Micro. and Immunol. (1992) 158:97-129).

Detailed Description Paragraph Right (157):
AAV has not been associated with the cause of any disease. AAV is not a transforming or oncogenic virus. AAV integration into chromosomes of human cell lines does not cause any significant alteration in the growth properties or morphological characteristics of the cells. These properties of AAV also recommend it as a potentially useful human gene therapy vector.

Detailed Description Paragraph Right (158):
AAV is also one of the few viruses that may integrate its DNA into non-dividing cells, e.g., pulmonary epithelial cells or muscle cells, and exhibits a high frequency of stable integration (see for example Flotte et al., (1992) Am. J. Respir. Cell. Mol. Biol. 7:349-356; Samulski et al., (1989) J. Virol. 63:3822-3828; and McLaughlin et al., (1989) J. Virol. 62:1963-1973). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous DNA is limited to about 4.5 kb. An AAV vector such as that described in Tratschin et al., (1985) Mol. Cell. Biol. 5:3251-3260 can be used to introduce DNA into cells. A variety of nucleic acids have been introduced into different cell types using AAV vectors (see for example Hermonat et al., (1984) PNAS U.S.A. 81:6466-6470; Tratschin et al., (1985) Mol. Cell. Biol. 4:2072-2081; Wondisford et al., (1988) Mol. Endocrinol. 2:32-39; Tratschin et al., (1984) J. Virol. 51:611-619; and Flotte et al., (1993) J. Biol. Chem. 268:3781-3790).

Detailed Description Paragraph Right (159):
The AAV-based expression vector to be used typically includes the 145 nucleotide AAV inverted terminal repeats (ITRs) flanking a restriction site that can be used for subcloning of the transgene, either directly using the restriction site available, or by excision of the transgene with restriction enzymes followed by blunting of the

ends, ligation of appropriate DNA linkers, restriction digestion, and ligation into the site between the ITRs. The capacity of AAV vectors is about 4.4 kb. The following proteins have been expressed using various AAV-based vectors, and a variety of promoter/enhancers: neomycin phosphotransferase, chloramphenicol acetyl transferase, Fanconi's anemia gene, cystic fibrosis transmembrane conductance regulator, and granulocyte macrophage colony-stimulating factor (Kotin, R. M., Human Gene Therapy 5:793-801,1994, Table I). A transgene incorporating the various DNA constructs of this invention can similarly be included in an AAV-based vector. As an alternative to inclusion of a constitutive promoter such as CMV to drive expression of the recombinant DNA encoding the fusion protein(s), e.g. fusion proteins comprising an activation domain or DNA-binding domain, an AAV promoter can be used (ITR itself or AAV p5 (Flotte, et al. J. Biol.Chem. 268:3781-3790, 1993)).

Detailed Description Paragraph Right (160):
Such a vector can be packaged into AAV virions by reported methods. For example, a human cell line such as 293 can be co-transfected with the AAV-based expression vector and another plasmid containing open reading frames encoding AAV rep and cap (which are obligatory for replication and packaging of the recombinant viral construct) under the control of endogenous AAV promoters or a heterologous promoter. In the absence of helper virus, the rep proteins Rep68 and Rep78 prevent accumulation of the replicative form, but upon superinfection with adenovirus or herpes virus, these proteins permit replication from the ITRs (present only in the construct containing the transgene) and expression of the viral capsid proteins. This system results in packaging of the transgene DNA into AAV virions (Carter, B. J., Current Opinion in Biotechnology 3:533-539, 1992; Kotin, R. M, Human Gene Therapy 5:793-801, 1994)). Typically, three days after transfection, recombinant AAV is harvested from the cells along with adenovirus and the contaminating adenovirus is then inactivated by heat treatment.

Detailed Description Paragraph Right (161):
Methods to improve the titer of AAV can also be used to express the transgene in an AAV virion. Such strategies include, but are not limited to: stable expression of the ITR-flanked transgene in a cell line followed by transfection with a second plasmid to direct viral packaging; use of a cell line that expresses AAV proteins inducibly, such as temperature-sensitive inducible expression or pharmacologically inducible expression. Alternatively, a cell can be transformed with a first AAV vector including a 5' ITR, a 3' ITR flanking a heterologous gene, and a second AAV vector which includes an inducible origin of replication, e.g., SV40 origin of replication, which is capable of being induced by an agent, such as the SV40 T antigen and which includes DNA sequences encoding the AAV rep and cap proteins. Upon induction by an agent, the second AAV vector may replicate to a high copy number, and thereby increased numbers of infectious AAV particles may be generated (see, e.g, U.S. Pat. No. 5,693,531 by Chiorini et al., issued Dec. 2, 1997. In yet another method for producing large amounts of recombinant AAV, a plasmid is used which incorporate the Epstein Barr Nuclear Antigen (EBNA) gene, the latent origin of replication of Epstein Barr virus (oriP) and an AAV genome. These plasmids are maintained as a multicopy extra-chromosomal elements in cells, such as in 293 cells. Upon addition of wild-type helper functions, these cells will produce high amounts of recombinant AAV (U.S. Pat. No. 5,691,176 by Lebkowski et al., issued Nov. 25, 1997). In another system, an AAV packaging plasmid is provided that allows expression of the rep gene, wherein the p5 promoter, which normally controls rep expression, is replaced with a heterologous promoter (U.S. Pat. No. 5,658,776, by Flotte et al., issued Aug. 19, 1997). Additionally, one may increase the efficiency of AAV transduction by treating the cells with an agent that facilitates the conversion of the single stranded form to the double stranded form, as described in Wilson et al., WO96/39530.

Detailed Description Paragraph Right (162):
AAV stocks can be produced as described in Hermonat and Muzyczka (1984) PNAS 81:6466, modified by using the pAAV/Ad described by Samulski et al. (1989) J. Virol. 63:3822. Concentration and purification of the virus can be achieved by reported methods such as banding in cesium chloride gradients, as was used for the initial report of AAV vector expression in vivo (Flotte, et al. J.Biol. Chem. 268:3781-3790,1993) or chromatographic purification, as described in O'Riordan et al., WO97/08298.

Detailed Description Paragraph Right (163):
Methods for in vitro packaging AAV vectors are also available and have the advantage that there is no size limitation of the DNA packaged into the particles (see, U.S. Pat. No. 5,688,676, by Zhou et al., issued Nov. 18, 1997). This procedure involves the preparation of cell free packaging extracts.

Detailed Description Paragraph Right (164):
For additional detailed guidance on AAV technology which may be useful in the practice of the subject invention, including methods and materials for the incorporation of a transgene, the propagation and purification of the recombinant AAV vector containing the transgene, and its use in transfecting cells and mammals, see e.g. Carter et al, U.S. Pat. No. 4,797,368 (Jan. 10, 1989); Muzyczka et al, U.S. Pat. No. 5,139,941 (Aug. 18, 1992); Lebkowski et al, U.S. Pat. No. 5,173,414 (Dec. 22, 1992); Srivastava, U.S. Pat. No. 5,252,479 (Oct. 12, 1993); Lebkowski et al, U.S. Pat. No. 5,354,678 (Oct. 11, 1994); Shenk et al, U.S. Pat. No. 5,436,146(Jul. 25, 1995); Chatterjee et al, U.S. Pat. No. 5,454,935 (Dec. 12, 1995), Carter et al WO 93/24641 (published Dec. 9, 1993), and Natsoulis, U.S. Pat. No. 5,622,856 (Apr. 22, 1997). Further information regarding AAVs and the adenovirus or herpes helper functions required can be found in the following articles.Berns and Bohensky (1987), "Adeno-Associated Viruses: An Update", Advanced in Virus Research, Academic Press, 33:243-306. The genome of AAV is described in Laughlin et al. (1983) "Cloning of infectious adeno-associated virus genomes in bacterial plasmids", Gene, 23: 65-73. Expression of AAV is described in Beaton et al. (1989) "Expression from the Adeno-associated virus p5 and p19 promoters is negatively regulated in trans by the rep protein", J. Virol., 63:4450-4454. Construction of rAAV is described in a number of publications: Tratschin et al. (1984) "Adeno-associated virus vector for high frequency integration, expression and rescue of genes in mammalian cells", Mol. Cell. Biol., 4:2072-2081; Hermonat and Muzyczka (1984) "Use of adeno-associated virus as a mammalian DNA cloning vector Transduction of neomycin resistance into mammalian tissue culture cells", Proc. Natl. Acad. Sci. U.S.A., 81 :6466-6470; McLaughlin et al. (1988) "Adeno-associated virus general transduction vectors: Analysis of Proviral Structures", J. Virol., 62:1963-1973; and Samulski et al. (1989) "Helper-free stocks of recombinant adeno-associated viruses: normal integration does quote viral gene expression", J. Virol., 63:3822-3828. Cell lines that can be transformed by rAAV are those described in Lebkowski et al. (1988) "Adeno-associated virus: a vector system for efficient introduction and integration of DNA into a variety of mammalian cell types", Mol. Cell. Biol., 8:3988-3996. "Producer" or "packaging" cell lines used in manufacturing recombinant retroviruses are described in Dougherty et al. (1989) J. Virol., 63:3209-3212; and Markowitz et al. (1988) J. Virol., 62:1120-1124.

Detailed Description Paragraph Right (165):
Hybrid Adenovirus-AAV vectors represented by an adenovirus capsid containing a nucleic acid comprising a portion of an adenovirus, and 5' and 3' ITR sequences from an AAV which flank a selected transgene under the control of a promoter. See e.g. Wilson et al, International Patent Application Publication No. WO 96/13598. This hybrid vector is characterized by high titer transgene delivery to a host cell and the ability to stably integrate the transgene into the host cell chromosome in the presence of the rep gene. This virus is capable of infecting virtually all cell types (conferred by its adenovirus sequences) and stable long term transgene integration into the host cell genome (conferred by its AAV sequences).

Detailed Description Paragraph Right (167):
The AAV sequences useful in the hybrid vector are viral sequences from which the rep and cap polypeptide encoding sequences are deleted and are usually the cis acting 5' and 3' ITR sequences. Thus, the AAV ITR sequences are flanked by the selected adenovirus sequences and the AAV ITR sequences themselves flank a selected transgene. The preparation of the hybrid vector is further described in detail in published PCT application entitled "Hybrid Adenovirus-AAV Virus and Method of Use Thereof", WO 96/13598 by Wilson et al.

Detailed Description Paragraph Right (168):
For additional detailed guidance on adenovirus and hybrid adenovirus-AAV technology which may be useful in the practice of the subject invention, including methods and

materials for the incorporation of a transgene, the propagation and purification of recombinant virus containing the transgene, and its use in transfecting cells and mammals, see also Wilson et al, WO 94/28938, WO 96/13597 and WO 96/26285, and references cited therein.

Detailed Description Paragraph Left (22):
AAV Vectors

Detailed Description Paragraph Left (23):
Hybrid Adenovirus-AAV Vectors

CLAIMS:

12. The vector of claim 11 wherein the vector is selected from the group consisting of adenoviral vectors, adeno-associated virus (AAV) vectors, retroviral vectors, hybrid adenovirus-AAV vectors, and herpes-simplex virus (HSV) vectors.

28. The composition of claim 18 wherein the recombinant virus is selected from the group consisting of adenovirus, AAV, retrovirus, hybrid adenovirus-AAV, and HSV.

35. The vector of claim 32 wherein the vector is selected from the group consisting of adenoviral vectors, AAV vectors, retroviral vectors, hybrid adenovirus-AAV vectors and HSV vectors.

47. The vector of claim 46 wherein the vector is selected from the group consisting of adenoviral vectors, AAV vectors, retroviral vectors, hybrid adenovirus-AAV vectors and HSV vectors.

50. The composition of claim 49, wherein at least one of the recombinant viruses is selected from the group consisting of adenovirus, AAV, retrovirus, hybrid adenovirus-AAV and HSV.

59. The composition of claim 56, wherein at least one of the recombinant viruses is selected from the group consisting of adenovirus, AAV, retrovirus, hybrid adenovirus-AAV and HSV.

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L3: Entry 10 of 11 File: USPT Sep 12, 2000

US-PAT-NO: 6117680
DOCUMENT-IDENTIFIER: US 6117680 A

TITLE: Compositions and methods for regulation of transcription

DATE-ISSUED: September 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Natesan; Sridaran	Chestnut Hill	MA		
Gilman; Michael Z.	Newton	MA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
ARIAD Gene Therapeutics, Inc.	Cambridge	MA			02

APPL-NO: 9/ 140149 [PALM]
DATE FILED: August 26, 1998

PARENT-CASE:
This application is a continuation-in-part of U.S. Ser. No. 09/126,009, filed Jul. 29, 1998, which is a continuation-in-part of Ser. No. 08/920,610, filed Aug. 27, 1997, now U.S. Pat. No. 6,015,709, which is a continuation-in-part of Ser. No. 08/918,401, filed Aug. 26, 1997, now abandoned, and also claims the priority benefit of International Application PCT/US97/15219, filed Aug. 27, 1997.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
WO	PCT/US97/15219	August 27, 1997

INT-CL: [7] C12 N 5/10, C12 N 15/63

US-CL-ISSUED: 435/455; 435/235.1, 435/320.1, 435/325, 435/456, 536/23.4
US-CL-CURRENT: 435/455; 435/235.1, 435/320.1, 435/325, 435/456, 536/23.4

FIELD-OF-SEARCH: 435/235.1, 435/320.1, 435/325, 435/455, 435/456, 536/23.1, 536/23.4

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5215909	June 1993	Soreq	435/325
☐	5573925	November 1996	Halazonetis	435/69.7
☐	5723329	March 1998	Mangelsdorf et al.	435/240.2
☐	5925523	July 1999	Dove et al.	435/6

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 94/10308	May 1994	WOX	
WO 97/12040	April 1997	WOX	

OTHER PUBLICATIONS

Zeng et al., (1997), Gene 185: 245-249.
Dang et al.,(1991), Mol Cell Biol 11:954-962.
Hunger et al. (1996), Blood, 87:4607-4617.
Qian et al., (1995), J. Virology 69:4037-4044.
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Zuo et al. (1994) Activation of the DNA-binding ability of human heat shock transcription factor 1 may involve the transition from an intramolecular to an intermolecular triple-stranded coiled-coil structure. Mol. Cell. Biol. 14:7557-7568, Nov. 1994.

ART-UNIT: 166
PRIMARY-EXAMINER: Schwartzman; Robert A.
ATTY-AGENT-FIRM: Berstein; David L. Hausdorff; Sharon F.

ABSTRACT:

The present invention relates to novel fusion proteins which activate transcription,

to nucleic acid constructs encoding the proteins and their use in the genetic engineering of cells.

62 Claims, 20 Drawing figures

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Search Results - Record(s) 11 through 11 of 11 returned.

☑ 11. Document ID: US 6015709 A

L3: Entry 11 of 11 File: USPT Jan 18, 2000

US-PAT-NO: 6015709
DOCUMENT-IDENTIFIER: US 6015709 A

TITLE: Transcriptional activators, and compositions and uses related thereto

Full | Title | CLS.11 | REF.11 | SEQ.11 | ATT.11

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Term	Documents
(2 NOT 1).USPT,PGPB,JPAB,EPAB,DWPI.	11
(L2 NOT L1).USPT,PGPB,JPAB,EPAB,DWPI.	11

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Search Results - Record(s) 1 through 10 of 11 returned.

☐ 1. Document ID: US 20020068815 A1

L3: Entry 1 of 11 File: PGPB Jun 6, 2002

PGPUB-DOCUMENT-NUMBER: 20020068815
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020068815 A1

TITLE: DAX-1 PROTEIN, METHODS FOR PRODUCTION AND USE THEREOF

PUBLICATION-DATE: June 6, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
MCCABE, EDWARD R. B.	PACIFIC PALISADES	CA	US	
GUO, WEIWEN	LOS ANGELES	CA	US	
BURRIS, THOMAS P.	GLEN GARDNER	NJ	US	
VILAIN, ERIC	LOS ANGELES	CA	US	

US-CL-CURRENT: 530/350; 435/69.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020049151 A1

L3: Entry 2 of 11 File: PGPB Apr 25, 2002

PGPUB-DOCUMENT-NUMBER: 20020049151
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020049151 A1

TITLE: Therapeutic approaches to diseases by suppression of the NURR subfamily of nuclear transcription factors

PUBLICATION-DATE: April 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Murphy, Evelyn	Dublin	TX	IE	
Conneely, Orla M.	Houston		US	
Fitzgerald, Oliver	Dublin		IE	
Bresnihan, Barry	Dublin		IE	

US-CL-CURRENT: 514/1; 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC
Draw Desc | Image

☐ 3. Document ID: US 20020004489 A1

L3: Entry 3 of 11 File: PGPB Jan 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020004489
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020004489 A1

TITLE: Retinoid receptor interacting polynucleotides, polypeptides, and antibodies

PUBLICATION-DATE: January 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Shi, Yanggu	Gaithersburg	MD	US	
Ruben, Steven M.	Olney	MD	US	

US-CL-CURRENT: 514/44; 435/325, 435/69.1, 530/350, 530/388.22, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 4. Document ID: US 20010049144 A1

L3: Entry 4 of 11 File: PGPB Dec 6, 2001

PGPUB-DOCUMENT-NUMBER: 20010049144
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010049144 A1

TITLE: Methods for high level expression of genes in primates

PUBLICATION-DATE: December 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rivera, Victor	Arlington	MA	US	
Zoltick, Philip	Wynnewood	PA	US	
Wilson, James M.	Gladwyne	PA	US	

US-CL-CURRENT: 435/456; 424/93.21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 5. Document ID: US 6406693 B1

L3: Entry 5 of 11 File: USPT Jun 18, 2002

US-PAT-NO: 6406693
DOCUMENT-IDENTIFIER: US 6406693 B1

TITLE: Cancer treatment methods using antibodies to aminophospholipids

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image

KWIC

☐ 6. Document ID: US 6342221 B1

L3: Entry 6 of 11 File: USPT Jan 29, 2002

US-PAT-NO: 6342221
DOCUMENT-IDENTIFIER: US 6342221 B1

TITLE: Antibody conjugate compositions for selectively inhibiting VEGF

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image

KWIC

☐ 7. Document ID: US 6342219 B1

L3: Entry 7 of 11 File: USPT Jan 29, 2002

US-PAT-NO: 6342219
DOCUMENT-IDENTIFIER: US 6342219 B1

TITLE: Antibody compositions for selectively inhibiting VEGF

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image

KWIC

☐ 8. Document ID: US 6312694 B1

L3: Entry 8 of 11 File: USPT Nov 6, 2001

US-PAT-NO: 6312694
DOCUMENT-IDENTIFIER: US 6312694 B1

TITLE: Cancer treatment methods using therapeutic conjugates that bind to aminophospholipids

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image

KWIC

☐ 9. Document ID: US 6214620 B1

L3: Entry 9 of 11 File: USPT Apr 10, 2001

US-PAT-NO: 6214620
DOCUMENT-IDENTIFIER: US 6214620 B1

TITLE: Inducible genetic suppression of cellular excitability

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image | KWIC

☑ 10. Document ID: US 6117680 A

L3: Entry 10 of 11 File: USPT Sep 12, 2000

US-PAT-NO: 6117680
DOCUMENT-IDENTIFIER: US 6117680 A

TITLE: Compositions and methods for regulation of transcription

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Draw Desc | Image | KWIC

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Term	Documents
(2 NOT 1).USPT,PGPB,JPAB,EPAB,DWPI.	11
(L2 NOT L1).USPT,PGPB,JPAB,EPAB,DWPI.	11

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155, 5
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            $0.00    0.072 DialUnits File410
     $0.00  Estimated cost File410
     $0.01  TELNET
     $0.01  Estimated cost this search
     $0.01  Estimated total session cost   0.226 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2002/Jun W3
*File 155: Daily alerts are now available. This file has
been reloaded. Accession numbers have changed.
  File   5:Biosis Previews(R)  1969-2002/Jun W3
         (c) 2002 BIOSIS

      Set  Items  Description
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? s rxr and retinoid?
            3293  RXR
           20798  RETINOID?
      S1    2710  RXR AND RETINOID?
? s s1 and aav
            2710  S1
            2095  AAV
      S2       0  S1 AND AAV
? s s1 and ecdysone?
            2710  S1
            5050  ECDYSONE?
      S3      36  S1 AND ECDYSONE?
? rd
...completed examining records
      S4      24  RD (unique items)
? t s4/3,ab/all

 4/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12844017   21454236   PMID: 11570505
  Bicistronic expression of ecdysone-inducible receptors in mammalian
cells.
  Wyborski D L; Bauer J C; Vaillancourt P
  Stratagene Cloning Systems, La Jolla, CA, USA.
  BioTechniques (United States)   Sep 2001,  31  (3)  p618-20, 622, 624,
ISSN 0736-6205   Journal Code: 8306785
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The recent emergence of inducible expression systems for mammalian cells
has greatly facilitated the in vivo analysis of gene function. The
ecdysone -inducible expression system is particularly attractive
because of (i) extremely low basal expression and high-level induced
expression, (ii) the lack of pleiotropic effects caused by the inducer or
activator, and (iii) the rapid penetrance and clearance of the inducer.
Here, we describe an improved receptor expression vector. The required
ecdysone receptor proteins (VgEcR and RXR) are co-expressed
from a bicistronic cytomegalovirus (CMV) expression cassette in the vector
pERV3. The CMV promoter in this vector can be readily replaced with a cell
type-specific promoter of interest. Using the ecdysone analogs,
muristerone A or ponasterone A, induction ratios of up to three orders of
magnitude were attained in the transient transfection assays and in a cell
line stably transformed with both pERV3 and an ecdysone-inducible
reporter vector. Fine control of luciferase expression was achieved by
varying both the induction time and inducer concentration. Here, we
```

describe a set of cell lines stably transformed with the vector pERV3, in which the **ecdysone** receptors are expressed at optimal levels for the high-level induction of gene expression.

4/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12554199 21448833 PMID: 11564603
Requirement of co-factors for the ligand-mediated activity of the insect ecdysteroid receptor in yeast.
Tran H T; Shaaban S; Askari H B; Walfish P G; Raikhel A S; Butt T R
LifeSensors Inc., 271 Great Valley Parkway, Malvern, Pennsylvania 19355, USA.
Journal of molecular endocrinology (England) Oct 2001, 27 (2) p191-209, ISSN 0952-5041 Journal Code: 8902617
Contract/Grant No.: AI-36959; AI; NIAID
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In insects, a steroid hormone 20-hydroxyecdysone has an important role in regulating critical events such as development and reproduction. The action of 20-hydroxyecdysone is mediated by its binding to the ecdysteroid receptor (EcR), which requires a heterodimeric partner, ultraspiracle protein (USP), a homologue of the **retinoid** X receptor (**RXR**). The EcR-USP heterodimer represents a functional receptor complex capable of initiating transcription of early genes. Our goal was to establish a ligand-dependent transactivation system in yeast utilizing an insect EcR-USP heterodimer. This has been achieved using mosquito Aedes aegypti AaEcR-USP. Expression of AaEcR alone, but not USP, resulted in constitutive transcription of the **ecdysone** reporter gene coupled with the Drosophila heat shock protein-27 **ecdysone** response elements. Removal of the N-terminal A/B domain of AaEcR abolished its constitutive transcription. Constitutive transcription was also eliminated in the presence of its heterodimeric partner, AaUSPa, AaUSPb or mammalian **RXR** . This suggests that the A/B domain is essential for the EcR ligand-independent transactivation and its interaction with the yeast transcription complex. A ligand-mediated transactivation of Aa(Delta A/B)EcR-USP or Aa(Delta A/B)EcR-**RXR** heterodimers in response to an ecdysteroid agonist RH-5992 was observed only in the presence of GRIP1, a mouse co-activator. In the presence of a co-repressor, SMRT, Aa(Delta A/B)EcR-USP heterodimer exhibited a ligand-dependent repression activity. In addition, ligand-dependent transactivation systems for spruce budworm and fruit fly **ecdysone** receptors were also reported. This is the first report establishing the requirements of co-factors for a highly efficient ligand-dependent function of the insect EcR-USP in yeast. These findings open a way to study insect EcR-USP structure and function and to identify ligands that are specific for a certain group of insects, such as mosquitoes.

4/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11292452 21329581 PMID: 11435614
Reconstruction of ligand-dependent transactivation of Choristoneura fumiferana **ecdysone** receptor in yeast.
Tran H T; Askari H B; Shaaban S; Price L; Palli S R; Dhadialla T S; Carlson G R; Butt T R
LifeSensors, Inc., Malvern, Pennsylvania 19355, USA.
Molecular endocrinology (Baltimore, Md.) (United States) Jul 2001, 15 (7) p1140-53, ISSN 0888-8809 Journal Code: 8801431
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Ecdysteroids play an important role in regulating development and reproduction in insects. Interaction of 20-hydroxyecdysone (20E) with **ecdysone** receptor (EcR) as a heterodimer with ultraspiracle (USP) protein triggers the activation of 20E-responsive genes. In this paper we describe a ligand-mediated transactivation system in yeast using the spruce budworm Choristoneura fumiferana **ecdysone** receptor (CfEcR). Coexpression of C. fumiferana USP (CfUSP) with CfEcR in yeast led to constitutive transcription of the reporter gene. However, deletion of the A/B domain of CfUSP abolished constitutive activity observed for the CfUSP:CfEcR complex. Replacement of USP with its mammalian homolog **retinoid** X receptors (RXRs) abolished the constitutive activity of the heterodimer but it did not restore EcR ligand-mediated transactivation. These data suggest that USP and its A/B domain play a role in the constitutive function of CfEcR:USP in yeast. A ligand-mediated transactivation was observed when GRIP1, a mouse coactivator gene, was added to EcR:**RXR** or EcR:DeltaA/BUSP complexes. Deletion of the A/B domain of EcR in the context of DeltaA/BEcR:**RXR** :GRIP1 or DeltaA/BEcR:DeltaA/BUSP:GRIP1 dramatically improved the ligand-dependent transactivation. This is the first example of highly efficient ligand-dependent transactivation of insect EcR in yeast. Analysis of transactivation activity of different ecdysteroidal compounds showed that the yeast system remarkably mimics the response observed in insect tissue culture cells and whole insect systems. The results open the way to develop assays that can be used to screen novel species-specific **ecdysone** agonist/antagonist insecticides.

4/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11110918 21117075 PMID: 11171988

The structure of the ultraspiracle ligand-binding domain reveals a nuclear receptor locked in an inactive conformation.

Clayton G M; Peak-Chew S Y; Evans R M; Schwabe J W
Medical Research Council, Laboratory of Molecular Biology, Cambridge CB2 2QH, United Kingdom.

Proceedings of the National Academy of Sciences of the United States of America (United States) Feb 13 2001, 98 (4) p1549-54, ISSN 0027-8424
Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Ultraspiracle (USP) is the invertebrate homologue of the mammalian **retinoid** X receptor (**RXR**). **RXR** plays a uniquely important role in differentiation, development, and homeostasis through its ability to serve as a heterodimeric partner to many other nuclear receptors. **RXR** is able to influence the activity of its partner receptors through the action of the ligand 9-cis retinoic acid. In contrast to **RXR** , USP has no known high-affinity ligand and is thought to be a silent component in the heterodimeric complex with partner receptors such as the **ecdysone** receptor. Here we report the 2.4-A crystal structure of the USP ligand-binding domain. The structure shows that a conserved sequence motif found in dipteran and lepidopteran USPs, but not in mammalian RXRs, serves to lock USP in an inactive conformation. It also shows that USP has a large hydrophobic cavity, implying that there is almost certainly a natural ligand for USP. This cavity is larger than that seen previously for most other nuclear receptors. Intriguingly, this cavity has partial occupancy by a bound lipid, which is likely to resemble the natural ligand for USP.

4/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10993353 20570511 PMID: 11114195
Identification of ligands and coligands for the **ecdysone**-regulated gene switch.
Saez E; Nelson M C; Eshelman B; Banayo E; Koder A; Cho G J; Evans R M
The Salk Institute for Biological Studies, Howard Hughes Medical Institute, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Dec 19 2000, 97 (26) p14512-7, ISSN 0027-8424
Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The **ecdysone**-inducible gene switch is a useful tool for modulating gene expression in mammalian cells and transgenic animals. We have identified inducers derived from plants as well as certain classes of insecticides that increase the versatility of this gene regulation system. Phytoecdysteroids share the favorable kinetics of steroids, but are inert in mammals. The gene regulation properties of one of these ecdysteroids have been examined in cell culture and in newly developed strains of **ecdysone** -system transgenic mice. Ponasterone A is a potent regulator of gene expression in cells and transgenic animals, enabling reporter genes to be turned on and off rapidly. A number of nonsteroidal insecticides have been identified that also activate the **ecdysone** system. Because the gene-controlling properties of the **ecdysone** switch are based on a heterodimer composed of a modified **ecdysone** receptor (VgEcR) and the **retinoid** X receptor (**RXR**), we have tested the effect of **RXR** ligands on the VgEcR/**RXR** complex. Used alone, **RXR** ligands display no activity on the **ecdysone** switch. However, when used in combination with a VgEcR ligand, **RXR** ligands dramatically enhance the absolute levels of induction. This property of the heterodimer has allowed the development of superinducer combinations that increase the dynamic range of the system.

4/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10838636 20397452 PMID: 10933926
Adenovirus-mediated inducible gene expression in vivo by a hybrid **ecdysone** receptor.
Hoppe U C; Marban E; Johns D C
Institute for Molecular Cardiobiology, Johns Hopkins University, Baltimore, Maryland 21205, USA.
Molecular therapy : the journal of the American Society of Gene Therapy (UNITED STATES) Feb 2000, 1 (2) p159-64, ISSN 1525-0016
Journal Code: 100890581
Contract/Grant No.: P50 HL52370; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Precise control of transgene expression would markedly facilitate certain applications of gene therapy. To regulate expression of a transferred gene in response to an exogenous compound in vivo, we modified the **ecdysone** -responsive system. We combined the advantages of the Drosophila (DmEcR) and the Bombyx **ecdysone** receptor (BmEcR) by creating a chimeric Drosophila/Bombyx **ecdysone** receptor (DB-EcR) that preserved the ability to bind to the modified **ecdysone** promoter without exogenous **retinoid** X receptor (**RXR**). In cultured cells,

DB-EcR effectively mediates ligand-dependent transactivation of a reporter gene at lower concentrations of the chemical **ecdysone** agonist GS-E than VgRXR (DmEcR + **RXR**). Transgene delivery in vivo was achieved by intramyocardial injection of recombinant adenovirus vectors in adult rats. Upon stimulation with GS-E, DB-EcR potently (>40-fold induction) activated gene expression in vivo while VgRXR was not induced. This hybrid **ecdysone** receptor represents an important new tool for in vivo transgene regulation with potentially diverse applications in somatic and germline transfer.

4/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10754415 20285345 PMID: 10824105
Structural and functional divergence of a nuclear receptor of the **RXR** family from the trematode parasite Schistosoma mansoni.
de Mendonca R L; Escriva H; Bouton D; Zelus D; Vanacker J M; Bonnelye E; Cornette J; Pierce R J; Laudet V
INSERM U 167, Institut Pasteur, Lille; CNRS UMR 49, Ecole Normale Superieure de Lyon, France.
European journal of biochemistry / FEBS (GERMANY) Jun 2000, 267 (11) p3208-19, ISSN 0014-2956 Journal Code: 0107600
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We describe the cloning and functional characterization of Schistosoma mansoni **retinoid** -X-receptor (SmRXR; NR2B4-B), a novel member of the nuclear receptor superfamily from S. mansoni, a homologue of vertebrate **retinoid** -X-receptor. The DNA-binding C domain of SmRXR shows 80% sequence identity to both human RXRalpha and Drosophila ultraspiracle (USP), but a much lower level of conservation of the ligand-binding E domain (22-25% identity). Phylogenetic analysis places SmRXR within the **RXR** group as an early offshoot of this clade. SmRXR mRNA is expressed at all life-cycle stages but at higher levels in the free-living larval stages. However, the SmRXR protein is expressed at markedly different levels, being almost absent from eggs while present at the highest concentration in schistosomula. Recombinant SmRXR fails to bind to the consensus direct repeat response elements, either alone, or as a heterodimer with mouse retinoic acid receptor alpha or the Drosophila **ecdysone** receptor. However, the use of chimaeric constructions shows that the C domain of SmRXR will bind to conventional response elements as a heterodimer, and that its specificity is modified by the presence of the D and E domains. In accordance with these results, native SmRXR failed to transactivate the transcription of a reporter gene after cotransfection of mammalian cell lines.

4/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10695901 20245468 PMID: 10783141
Sustained mammary gland-directed, ponasterone A-inducible expression in transgenic mice.
Albanese C; Reutens A T; Bouzahzah B; Fu M; D'Amico M; Link T; Nicholson R; Depinho R A; Pestell R G
The Albert Einstein Cancer Center, Department of Developmental and Molecular Biology, Department of Medicine and. Department of Biochemistry, Albert Einstein College of Medicine, Bronx, NY 10461, USA.
FASEB journal : official publication of the Federation of American Societies for Experimental Biology (UNITED STATES) May 2000, 14 (7) p877-84, ISSN 0892-6638 Journal Code: 8804484
Contract/Grant No.: 5-P30-CA13330-26; CA; NCI; R29CA70896-01; CA; NCI;

RO1CA75503; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The ability to regulate temporal- and spatial-specific expression of target genes in transgenic mice will facilitate analysis of gene function and enable the generation of murine models of human diseases. The genetic analysis of mammary gland tumorigenesis requires the development of mammary gland-specific transgenics, which are tightly regulated throughout the adult mammary epithelium. Analysis of genes implicated in mammary gland tumorigenesis has been hampered by mosaic transgene expression and the findings that homozygous deletion of several candidate genes (cyclin D1, Stat5A, prolactin receptor) abrogates normal mammary gland development. We describe the development of transgenic mouse lines in which sustained transgene expression was inducibly regulated, both specifically and homogeneously, in the adult mammary gland epithelium. Transgenes encoding RXRalpha and a chimeric **ecdysone** receptor under control of a modified MMTV-LTR, which targets mammary gland expression, were used. These transgenic 'receptor' lines were crossed with transgenic 'enhancer' lines in which the **ecdysone/RXR** binding site induced ligand-dependent expression of transgenic beta-galactosidase. Pharmacokinetic analysis of a highly bioactive ligand (ponasterone A), identified through screening ecdysteroids from local plants, demonstrated sustained release and transgene expression in vivo. This transgenic model with both tightly regulated and homogeneous transgene expression, which was sustained in vivo using ligands readily extracted from local flora, has broad practical applicability for genetic analysis of mammary gland disease.

4/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10693211 20239128 PMID: 10778857

Molecular chaperones activate the Drosophila **ecdysone** receptor, an **RXR** heterodimer.

Arbeitman M N; Hogness D S
Department of Developmental Biology, Stanford University School of Medicine, California 94305, USA.

Cell (UNITED STATES) Mar 31 2000, 101 (1) p67-77, ISSN 0092-8674 Journal Code: 0413066
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The steroid hormone 20-hydroxyecdysone coordinates the stages of Drosophila development by activating a nuclear receptor heterodimer consisting of the **ecdysone** receptor, EcR, and the Drosophila **RXR** receptor, USP. We show that EcR/USP DNA binding activity requires activation by a chaperone heterocomplex like that required for activation of the vertebrate steroid receptors, but not previously shown to be required for activation of **RXR** heterodimers. Six proteins normally present in the chaperone complex were individually purified and shown to be sufficient for this activation. We also show that two of the six (Hsp90 and Hsc70) are required in vivo for **ecdysone** receptor activity, and that EcR is the primary target of the chaperone complex.

4/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10447340 99432385 PMID: 10502114

The sequence of Locusta **RXR** , homologous to Drosophila Ultraspiracle, and its evolutionary implications.

Hayward D C; Bastiani M J; Trueman J W; Truman J W; Riddiford L M; Ball E E

Molecular Genetics and Evolution Group, Research School of Biological Sciences, Australian National University, P.O. Box 475, Canberra, ACT 2601, Australia.

Development genes and evolution (GERMANY) Sep 1999, 209 (9) p564-71, ISSN 0949-944X Journal Code: 9613264

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The cellular response to steroid hormones is mediated by nuclear receptors which act by regulating transcription. In Drosophila melanogaster, the receptor for the insect molting hormone, 20-hydroxyecdysone, is a heterodimer composed of the **Ecdysone** Receptor and Ultraspiracle (USP) proteins. The DNA binding domains of arthropod USPs and their vertebrate homologs, the **retinoid** X receptor (**RXR**) family, are highly conserved. The ligand binding domain sequences, however, divide into two distinct groups. One group consists of sequences from members of the holometabolous higher insect orders Diptera and Lepidoptera, the other of sequences from vertebrates, a crab and a tick. We here report the sequence of an **RXR** /USP from the hemimetabolous orthopteran, Locusta migratoria. The locust **RXR**/USP ligand binding domain clearly falls in the vertebrate-crab-tick rather than the dipteran-lepidopteran group. The reason for the evolutionarily abrupt divergence of the dipteran and lepidopteran sequences is unknown, but it could be a change in the type of ligand bound or the loss of ligand altogether.

4/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10226921 99223567 PMID: 10207062

Alien, a highly conserved protein with characteristics of a corepressor for members of the nuclear hormone receptor superfamily.

Dressel U; Thormeyer D; Altincicek B; Paululat A; Eggert M; Schneider S; Tenbaum S P; Renkawitz R; Baniahmad A

Genetisches Institut der Justus-Liebig-Universitat, D-35392 Giessen, Germany.

Molecular and cellular biology (UNITED STATES) May 1999, 19 (5) p3383-94, ISSN 0270-7306 Journal Code: 8109087

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Some members of nuclear hormone receptors, such as the thyroid hormone receptor (TR), silence gene expression in the absence of the hormone. Corepressors, which bind to the receptor's silencing domain, are involved in this repression. Hormone binding leads to dissociation of corepressors and binding of coactivators, which in turn mediate gene activation. Here, we describe the characteristics of Alien, a novel corepressor. Alien interacts with TR only in the absence of hormone. Addition of thyroid hormone leads to dissociation of Alien from the receptor, as shown by the yeast two-hybrid system, glutathione S-transferase pull-down, and coimmunoprecipitation experiments. Reporter assays indicate that Alien increases receptor-mediated silencing and that it harbors an autonomous silencing function. Immune staining shows that Alien is localized in the cell nucleus. Alien is a highly conserved protein showing 90% identity between human and Drosophila. Drosophila Alien shows similar activities in that it interacts in a hormone-sensitive manner with TR and harbors an autonomous silencing function. Specific interaction of Alien is seen with Drosophila nuclear hormone receptors, such as the **ecdysone** receptor and Seven-up, the Drosophila homologue of COUP-TF1, but not with retinoic

acid receptor, **RXR** /USP, DHR 3, DHR 38, DHR 78, or DHR 96. These properties, taken together, show that Alien has the characteristics of a corepressor. Thus, Alien represents a member of a novel class of corepressors specific for selected members of the nuclear hormone receptor superfamily.

4/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10059236 99026060 PMID: 9806919
The **RXR** homolog ultraspiracle is an essential component of the Drosophila **ecdysone** receptor.
Hall B L; Thummel C S
Howard Hughes Medical Institute, University of Utah, Salt Lake City, UT 84112-5331, USA.
Development (Cambridge, England) (ENGLAND) Dec 1998, 125 (23) p4709-17, ISSN 0950-1991 Journal Code: 8701744
Contract/Grant No.: F32 GM17875; GM; NIGMS; S10RR0-10489; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Pulses of the steroid hormone **ecdysone** function as key temporal signals during insect development, coordinating the major postembryonic developmental transitions, including molting and metamorphosis. In vitro studies have demonstrated that the EcR **ecdysone** receptor requires an **RXR** heterodimer partner for its activity, encoded by the ultraspiracle (usp) locus. We show here that usp exerts no apparent function in mid-third instar larvae, when a regulatory hierarchy prepares the animal for the onset of metamorphosis. Rather, usp is required in late third instar larvae for appropriate developmental and transcriptional responses to the **ecdysone** pulse that triggers puparium formation. The imaginal discs in usp mutants begin to evert but do not elongate or differentiate, the larval midgut and salivary glands fail to undergo programmed cell death and the adult midgut fails to form. Consistent with these developmental phenotypes, usp mutants show pleiotropic defects in **ecdysone**-regulated gene expression at the larval-prepupal transition. usp mutants also recapitulate aspects of a larval molt at puparium formation, forming a supernumerary cuticle. These observations indicate that usp is required for **ecdysone** receptor activity in vivo, demonstrate that the EcR/USP heterodimer functions in a stage-specific manner during the onset of metamorphosis and implicate a role for usp in the decision to molt or pupariate in response to **ecdysone** pulses during larval development.

4/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09867968 98298162 PMID: 9632709
Isolation and characterization of a novel coactivator protein, NCoA-62, involved in vitamin D-mediated transcription.
Baudino T A; Kraichely D M; Jefcoat S C; Winchester S K; Partridge N C; MacDonald P N
Department of Pharmacological and Physiological Science, Program in Cell and Molecular Biology, St. Louis University Health Sciences Center, St. Louis, Missouri 63104, USA.
Journal of biological chemistry (UNITED STATES) Jun 26 1998, 273 (26) p16434-41, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: R01DK50348; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed

The vitamin D receptor (VDR) forms a heterodimeric complex with **retinoid** X receptor (**RXR**) and binds to vitamin D-responsive promoter elements to regulate the transcription of specific genes or gene networks. The precise mechanism of transcriptional regulation by the VDR. **RXR** heterodimer is not well understood, but it may involve interactions of VDR.**RXR** with transcriptional coactivator or corepressor proteins. Here, a yeast two-hybrid strategy was used to isolate proteins that selectively interacted with VDR and other nuclear receptors. One cDNA clone designated NCoA-62, encoded a 62, 000-Da protein that is highly related to BX42, a Drosophila melanogaster nuclear protein involved in **ecdysone**-stimulated gene expression. Yeast two-hybrid studies and in vitro protein-protein interaction assays using glutathione S-transferase fusion proteins demonstrated that NCoA-62 formed a direct protein-protein contact with the ligand binding domain of VDR. Coexpression of NCoA-62 in a vitamin D-responsive transient gene expression system augmented 1, 25-dihydroxyvitamin D3-activated transcription, but it had little or no effect on basal transcription or gal4-VP16-activated transcription. NCoA-62 also interacted with **retinoid** receptors, and its expression enhanced retinoic acid-, estrogen-, and glucocorticoid-mediated gene expression. These data indicate that NCoA-62 may be classified into an emerging set of transcriptional coactivator proteins that function to facilitate vitamin D- and other nuclear receptor-mediated transcriptional pathways.

4/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09696117 98121975 PMID: 9460643

Evolution of the nuclear receptor superfamily: early diversification from an ancestral orphan receptor.

Laudet V

URA1160 du CNRS Oncologie Moleculaire, Institut de Biologie de Lille, Institut Pasteur de Lille, France.

Journal of molecular endocrinology (ENGLAND) Dec 1997, 19 (3) p207-26, ISSN 0952-5041 Journal Code: 8902617

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

From a database containing the published nuclear hormone receptor (NR) sequences I constructed an alignment of the C, D and E domains of these molecules. Using this alignment, I have performed tree reconstruction using both distance matrix and parsimony analysis. The robustness of each branch was estimated using bootstrap resampling methods. The trees constructed by these two methods gave congruent topologies. From these analyses I defined six NR subfamilies: (i) a large one clustering thyroid hormone receptors (TRs), retinoic acid receptors (RARs), peroxisome proliferator-activated receptors (PPARs), vitamin D receptors (VDRs) and **ecdysone** receptors (EcRs) as well as numerous orphan receptors such as RORs or Rev-erbs; (ii) one containing **retinoid** X receptors (RXRs) together with COUP, HNF4, tailless, TR2 and TR4 orphan receptors; (iii) one containing steroid receptors; (iv) one containing the NGFIB orphan receptors; (v) one containing FTZ-F1 orphan receptors; and finally (vi) one containing to date only one gene, the GCNF1 orphan receptor. The relationships between the six subfamilies are not known except for subfamilies I and IV which appear to be related. Interestingly, most of the liganded receptors appear to be derived when compared with orphan receptors. This suggests that the ligand-binding ability of NRs has been gained by orphan receptors during the course of evolution to give rise to the presently known receptors. The distribution into six subfamilies correlates with the known abilities of the various NRs to bind to DNA as homo- or heterodimers. For example, receptors heterodimerizing efficiently with **RXR** belong to the first or the fourth subfamilies. I suggest that the ability to heterodimerize

evolved once, just before the separation of subfamilies I and IV and that the first NR was able to bind to DNA as a homodimer. From the study of NR sequences existing in vertebrates, arthropods and nematodes, I define two major steps of NR diversification: one that took place very early, probably during the multicellularization event leading to all the metazoan phyla, and a second occurring later on, corresponding to the advent of vertebrates. Finally, I show that in vertebrate species the various groups of NRs accumulated mutations at very different rates.

4/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09326606 97225943 PMID: 9122185
Coexpression of nuclear receptor partners increases their solubility and biological activities.
Li C; Schwabe J W; Banayo E; Evans R M
The Salk Institute for Biological Studies, Gene Expression Laboratory, La Jolla, CA 92037, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Mar 18 1997, 94 (6) p2278-83, ISSN 0027-8424 Journal Code: 7505876
Contract/Grant No.: GM 26444; GM; NIGMS; HD 27183; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The biological activities of the **retinoids** are mediated by two nuclear hormone receptors: the retinoic acid receptor (RAR) and the **retinoid**-X receptor (**RXR**). **RXR** (and its insect homologue ultraspiracle) is a common heterodimeric partner for many other nuclear receptors, including the insect **ecdysone** receptor. As part of a continuing analysis of nuclear receptor function, we noticed that, whereas **RXR** can be readily expressed in Escherichia coli to produce soluble protein, many of its heterodimeric partners cannot. For example, overexpression of RAR results mostly in inclusion bodies with the residual soluble component unable to interact with **RXR** or ligand efficiently. Similar results are seen with other **RXR**/ultraspiracle partners. To overcome these problems, we designed a novel double cistronic vector to coexpress **RXR** and its partner ligand-binding domains in the same bacterial cell. This resulted in a dramatic increase in production of soluble and apparently stable heterodimer. Hormone-binding studies using the purified **RXR** -RAR heterodimer reveal increased ligand-binding capacity of both components of 5- to 10-fold, resulting in virtually complete functionality. Based on these studies we find that bacterially expressed receptors can exist in one of three distinct states: insoluble, soluble but unable to bind ligand, or soluble with full ligand-binding capacity. These results suggest that coexpression may represent a general strategy for biophysical and structural analysis of receptor complexes.

4/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08525389 95280959 PMID: 7760852
Isolation of proteins that interact specifically with the **retinoid** X receptor: two novel orphan receptors.
Seol W; Choi H S; Moore D D
Department of Molecular Biology, Massachusetts General Hospital, Boston, 02114, USA.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Jan 1995, 9 (1) p72-85, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: DK-43382; DK; NIDDK
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We have used a yeast genetic system to isolate cDNAs encoding proteins that specifically interact with the ligand-binding domain of human **retinoid** X receptor-alpha (**RXR** alpha). A number encoded portions of two known **RXR** heterodimer partners, the retinoic acid receptor (RAR) and the peroxisome proliferator activated receptor. Of four additional **RXR**-interacting proteins (RIPs) selected for further study two, RIP14 and RIP15, are previously unidentified orphan members of the nuclear receptor superfamily. Two others, RIP110 and RIP13, do not show significant similarities to previously reported proteins. RIP110 interacts with LexA-**RXR** only in yeast cells grown in the presence of the **RXR** ligand 9-cis-RA, while the interaction of the four receptor superfamily members and RIP13 is unaffected by the presence or absence of 9-cis-RA. RIP110 and RIP13 also interact in yeast with several other members of the receptor superfamily, but RIP14 and RIP15 interact only with **RXR** . Analysis of larger cDNA clones demonstrates that there are at least two isoforms of RIP14 that differ in the N-terminal (A and B) and hinge (D) domains. Northern blot analysis indicates that RIP14 is expressed specifically in liver and kidney, while RIP15 is expressed in every tissue tested. Both RIP14 and 15 bind as heterodimers with **RXR** to the RA response element (RARE) from the promoter of the RAR beta 2 isoform (the beta RARE), and RIP14 and **RXR** heterodimers also bind the **ecdysone** response element from the Drosophila heat shock protein 27 promoter. Both heterodimers also bind to several synthetic RAREs and other elements. In cotransfections, neither RIP14 nor RIP15 trans-activates a reporter containing multiple copies of the beta RARE under any of a variety of conditions, suggesting that their activities are dependent on the binding of as yet unidentified specific ligands or on activation by other processes.

4/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08449990 95199298 PMID: 7892230

OR-1, a member of the nuclear receptor superfamily that interacts with the 9-cis-retinoic acid receptor.

Teboul M; Enmark E; Li Q; Wikstrom A C; Pelto-Huikko M; Gustafsson J A
Center for Biotechnology, Karolinska Institute, NOVUM, Huddinge, Sweden.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Mar 14 1995, 92 (6) p2096-100, ISSN 0027-8424
Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We have cloned a member of the nuclear receptor superfamily. The cDNA was isolated from a rat liver library and encodes a protein of 446 aa with a predicted mass of 50 kDa. This clone (OR-1) shows no striking homology to any known member of the steroid/thyroid hormone receptor superfamily. The most related receptor is the **ecdysone** receptor and the highest homologies represent < 10% in the amino-terminal domain, between 15-37% in the carboxyl-terminal domain and 50-62% in the DNA binding domain. The expression of OR-1 appears to be widespread in both fetal and adult rat tissues. Potential DNA response elements composed of a direct repeat of the hexameric motif AGGTCA spaced by 0-6 nt were tested in gel shift experiments. OR-1 was shown to interact with the 9-cis-retinoic acid receptor (**retinoid** X receptor, **RXR**) and the OR-1/**RXR** complex to bind to a direct repeat spaced by 4 nt (DR4). In transfection experiments, OR-1 appears to activate **RXR**-mediated function through the DR4. Therefore OR-1 might modulate 9-cis-retinoic acid signaling by interacting with **RXR**.

4/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07695075 93218726 PMID: 8385270
Heterodimerization of the Drosophila **ecdysone** receptor with **retinoid** X receptor and ultraspiracle.
Thomas H E; Stunnenberg H G; Stewart A F
Gene Expression Programme, EMBL, Heidelberg, Germany.
Nature (ENGLAND) Apr 1 1993, 362 (6419) p471-5, ISSN 0028-0836 Journal Code: 0410462
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Ecdysone in Drosophila has been a paradigm for steroid hormones since its ability to induce gene activity directly was demonstrated by its effects on moulting and polytene chromosome puffing. The **ecdysone** receptor (EcR) was recently confirmed as a member of the nuclear receptor superfamily by cloning and characterization in a Drosophila cell line. Here we show that EcR needs to heterodimerize with either the **retinoid** X receptor (**RXR**) or its Drosophila homologue, ultraspiracle (USP), for DNA binding and transactivation. These results place the **ecdysone** receptor in the heterodimerizing class of the nuclear receptor superfamily and demonstrate that the role of **RXR**/USP as a central and promiscuous partner in mediating the activity of these receptors is highly conserved. Whereas EcR-USP DNA-binding activity is unaffected by hormone, EcR-**RXR** DNA-binding activity is stimulated by either ecdysteroid or 9-cis-retinoic acid, demonstrating that hormone can play a role in heterodimer stabilization.

4/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07481173 93008244 PMID: 1327536
Drosophila ultraspiracle modulates **ecdysone** receptor function via heterodimer formation.
Yao T P; Segraves W A; Oro A E; McKeown M; Evans R M
Howard Hughes Medical Institute, La Jolla, California.
Cell (UNITED STATES) Oct 2 1992, 71 (1) p63-72, ISSN 0092-8674 Journal Code: 0413066
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The vertebrate **retinoid** X receptor (**RXR**) has been implicated in the regulation of multiple hormonal signaling pathways through the formation of heteromeric receptor complexes that bind DNA with high affinity. We now demonstrate that ultraspiracle (usp), a Drosophila **RXR** homolog, can substitute for **RXR** in stimulating the DNA binding of receptors for retinoic acid, T3, vitamin D, and peroxisome proliferator activators. These observations led to the search and ultimate identification of the **ecdysone** receptor (EcR) as a Drosophila partner of usp. Together, usp and EcR bind DNA in a highly cooperative fashion. Cotransfection of both EcR and usp expression vectors is required to render cultured mammalian cells **ecdysone** responsive. These results implicate usp as an integral component of the functional EcR. By demonstrating that receptor heterodimer formation precedes the divergence of vertebrate and invertebrate lineages, these data underscore a central role for **RXR** and its homolog usp in the evolution and control of the nuclear receptor-based endocrine system.

4/3,AB/20 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13565202 BIOSIS NO.: 200200194023
Analyzing the repressive function of Ultraspiracle, the Drosophila **RXR**, in Drosophila eye development.
AUTHOR: Ghbeish Nora; McKeown Michael(a)
AUTHOR ADDRESS: (a)Molecular Biology and Virology Laboratory, Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA, 92037**USA
JOURNAL: Mechanisms of Development 111 (1-2):p89-98 February, 2002
MEDIUM: print
ISSN: 0925-4773
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Response to the insect hormone **ecdysone** is mediated by a nuclear receptor complex containing Ultraspiracle (USP) and the **Ecdysone** Receptor (EcR). Among other phenotypes, loss of functional USP in Drosophila eye development results in an accelerated morphogenetic furrow, although loss of **ecdysone** arrests the furrow. We have shown that USP both represses and activates a gene affecting furrow movement, the **ecdysone**-responsive Z1 isoform of Broad-Complex, and we report additional usp mutant phenotypes. Using targeted replacement of USP to rescue usp mutant clones in the eye, we have mapped various USP functions and tested whether the USP nuclear receptor has an activating as well as a repressive effect on furrow movement. Furrow movement and related phenotypes are rescued by the presence of USP in a limited domain near the furrow while other phenotypes are rescued by USP expression posterior to the furrow. Our data indicate roles for USP activity at multiple developmental stages and help explain why loss of functional USP leads to furrow advancement while loss of **ecdysone** stops furrow movement.

2002

4/3,AB/21 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13284912 BIOSIS NO.: 200100492061
Comparison of adenylyl cyclase stimulation by 5-HT4(b) and 5-HT7(a) receptors using the **Ecdysone**-Inducible Mammalian Expression System.
AUTHOR: Bruheim S(a); Andressen K W(a); Krobert K A(a); Levy F O(a)
AUTHOR ADDRESS: (a)MSD Cardiovascular Res. Ctr. and Dept. of Pharmacol., Univ. of Oslo, Oslo**Norway
JOURNAL: Society for Neuroscience Abstracts 27 (1):p690 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The serotonin (5-HT) receptors 5-HT4 and 5-HT7 are G-protein coupled receptors that activate adenylyl cyclase (AC) and exist in several splice variants differing only in their intracellular carboxyl terminal tails. We wanted to determine if activation of AC differed between the 5-HT4(b) and 5-HT7(a) receptors. Comparison of receptor function using constitutive expression systems can be confounded by

different receptor expression levels and clonal cell line differences. By using the **Ecdysone**-Inducible Mammalian Expression System we could reproducibly express varying levels of receptor in the same clonal cell line. This system utilizes a heterodimer (VgRxR) of the modified **ecdysone** receptor (VgEcR) from Drosophila and the retionoid X receptor (**RXR**). This receptor binds a hybrid **ecdysone** response element (E/GRE) in the presence of the synthetic analog of **ecdysone**, ponasterone A. HEK293 cells stably expressing the heterodimer VgRxR receptor were stably transfected with a vector containing the coding regions for 5-HT4(b) and 5-HT7(a) receptors downstream of the E/GRE. Radioligand binding revealed low constitutive expression of both receptors, which could be titrated up to 3.7 pmol/mg protein with ponasterone A. Preliminary data indicate that constitutive AC activity and potency (EC50) of 5-HT are receptor level dependent at the 5-HT4(b) receptor but not at the 5-HT7(a) receptor. Additionally, the 5-HT7(a) receptor activated AC more efficiently than the 5-HT4(b) receptor over a wide range of expression levels. Comparative studies on inverse agonism are ongoing.

2001

4/3,AB/22 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12174691 BIOSIS NO.: 199900469540
Characterization of EcR and **RXR** homologues in the ixodid tick, Amblyomma americanum (L.).
AUTHOR: Palmer M J(a); Harmon M A; Laudet V
AUTHOR ADDRESS: (a)Department of Entomology and Plant Pathology, Oklahoma State University, 127 Noble Research Center, Stillwater, OK, 74078**USA
JOURNAL: American Zoologist 39 (4):p747-757 Sept., 1999
ISSN: 0003-1569
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Ecdysteroid hormones have been shown to regulate growth and development in insects, chelicerates and crustaceans. While they presumably mediate analogous functions in all arthropods, their action outside Insecta is poorly understood. Ecdysteroid receptors are heterodimeric proteins composed of two nuclear receptor superfamily members, the **ecdysone** receptor (EcR) and Ultraspiracle (USP), the invertebrate homologue of **retinoid** x receptors (RXRs). When paired, EcR/USP dimers function as ligand-activated transcription factors, binding to DNA response elements in target genes and activating transcription. A curious feature of the insect EcR and USP homologues isolated to date is the striking degree of heterogeneity in both EcR and USP proteins, relative to vertebrate nuclear receptor homologues. This feature has raised a number of questions regarding their evolution and functional equivalence. To examine the question of ecdysteroid action in ixodid ticks, we isolated chelicerate EcR and RXRhomologues from the ixodid tick, Amblyomma americanum. Like insects, ticks possess a single EcR homologue that encodes multiple protein isoforms. However, ticks possess at least two **RXR** genes that encode proteins with greater overall similarity to vertebrate RXRs. While tick EcR and **RXR** proteins can partner to form functional ecdysteroid receptors, the DNA and ligand binding domains of tick EcR and **RXR** proteins are quite divergent, and suggest that there may be important functional differences in both DNA and ligand binding of tick ecdysteroid receptors.

1999

4/3,AB/23 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09500413 BIOSIS NO.: 199497508783
Phylogeny of the steroid receptor superfamily.
AUTHOR: Detera-Wadleigh Sevilla D(a); Fanning Thomas G
AUTHOR ADDRESS: (a)Clinical Neurogenetics Branch, National Inst. Mental Health, Bethesda, MD 20892**USA
JOURNAL: Molecular Phylogenetics and Evolution 3 (3):p192-205 1994
ISSN: 1055-7903
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The phylogenetic relationships of 56 nuclear hormone receptors from both invertebrates and vertebrates were determined by the parsimony method (PAUP). The consensus tree suggests that the ancestral gene diverged into five major subfamilies, each of which evolved into at least one cluster of related molecules. These subfamilies are represented by: (i) thyroid hormone receptors (TR); (ii) steroid receptors (SR); (iii) retinoic acid receptors (RAR), **retinoid** X receptors (**RXR**), and the chicken ovalbumin upstream promoter transcription factor 1 (COUP) group; (ix) peroxisome proliferator-activated receptors (PPAR); and (v) vitamin D receptor (VDR) and knirps (kni) group. Although the neighbor-joining (N-J) method clustered the receptors into a greater number of subfamilies, it was evident that the components of the terminal receptor subgroups were similar to those found in the PAUP tree. These terminal clusters might then represent phylogenetically stable relationships. The positions of some orphan receptors were perturbed when a different algorithm was employed in the analysis. Both PAUP and N-J evolutionary trees showed that the receptors within the subgroups of a major sublineage tend to recognize hormones of very similar structure. This finding suggests that the relative phylogenetic position of orphans to well-characterized receptors might be exploited to predict the type of ligand they would recognize.

1994

4/3,AB/24 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09153548 BIOSIS NO.: 199497161918
Identification of **RXR** homologs in Dirofilaria immitis and C. elegans.
AUTHOR: Hough David M; Richer Jennifer; Maina Claude V
AUTHOR ADDRESS: New Engl. Biolabs., Beverly, MA 01915**USA
JOURNAL: Journal of Cellular Biochemistry Supplement 0 (18B):p378 1994
CONFERENCE/MEETING: Keystone Symposium on Steroid/Thyroid/Retinoic Acid Super Gene Family Taos, New Mexico, USA February 7-13, 1994
ISSN: 0733-1959
RECORD TYPE: Citation
LANGUAGE: English
1994